

REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claim Amendments

Claims 18 and 19 have been amended to incorporate the limitations of claim 17, and to recite the specific compounds for which pharmacological data is provided in the specification.

Claim 20 has been amended to make editorial changes.

Claim 21 has been amended to incorporate the limitations of claim 17.

Claim 22 has been amended to recite the particular compounds which are also recited in claim 21.

Claim 17 has been cancelled, without prejudice or disclaimer.

Therefore, no new matter has been added to the application by these amendments.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 17 and 22 under 35 U.S.C. § 112, second paragraph is respectfully traversed.

The Examiner takes the position that the “[t]he claim terms ‘5-HT₃ antagonistic agent’ and ‘5-HT_{1A} agonistic agent’ [are] unclear, because it is not known by the rejected claims the structure of the compounds these terms are meant to describe.”

As discussed above, claim 17 has been cancelled, without prejudice or disclaimer. As also discussed above, claim 22 has been amended to limit the “5-HT₃ antagonistic agent” to alosetron, granisetron, azasetron, tropisetron, ramosetron, ondansetron, leriisetron, cilansetron, itasetron, indisetron, dolasetron and (R)-zacopride, and to limit the “5-HT_{1A} agonistic agent” to tandospirone, as also recited in Claim 21.

Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 17-22 and 25 under 35 U.S.C. § 112, first paragraph, is respectfully traversed.

The Examiner takes the position that although the specification is enabling for pyrimidine derivatives of formula (I) in which ring A is saturated, unsaturated or partially saturated carbohexyl group, X₁ is amino or methyl, X₂ is hydrogen, Y is a direct bond, n is 3, and Ar is the group represented by the second formula listed, the specification is not enabling for compounds of any other permutation of formula (I).

Applicants respectfully disagree with the Examiner's position. The Examiner appears to only consider Table D of the specification, which provides results in action of several compounds on defecation under stress. However, there is additional data provided throughout the specification which does not appear to have been considered by the Examiner. For example, Table A-1 on pages 48-49 of the specification provide evidence that compounds within the scope of Applicants' claims inhibit both the 5-HT_{1A} and the 5-HT₃ receptors. Applicants have then chosen a sampling from this large Table to demonstrate that compounds which inhibit both the 5-HT_{1A} and the 5-HT₃ receptors do provide action on defecation under stress.

Applicants respectfully request that the Examiner consider all of the data in the specification when determining whether the claims are enabled.

Additionally, the rejection of claims 17 and 22 has been overcome by the previously discussed amendments.

With regard to claims 18 and 19, as discussed previously, these claims have been amended to recite the compounds for which pharmacological data is provided in the specification. Thus, the rejection of these claims has also been overcome.

With regard to claims 20, 21 and 25, Applicants respectfully assert that these claims are enabled by the specification, as the claims recite particular compounds, for which pharmacological data is provided in the specification.

Accordingly, the Examiner is respectfully requested to reconsider the enablement

rejection, in view of the claim amendments, as well as all of the data presented in the specification.

Rejection Under 35 U.S.C. § 103

The rejection of claims 1-2, 7, 9-11, 13 and 15 stand rejected under 35 U.S.C. § 103 (a) as being unpatentable over Matsuoka et al. (CA 2431406) is respectfully traversed.

The Examiner states that Applicants have failed to discuss the case law that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results.

Accordingly, Applicants present the following comments.

Compounds whose nitrogen atom at the 3-position of pyrimidine ring is unsubstituted, like those of Matsuoka et al., generally have a low affinity for the 5-HT_{1A} receptor. For the treatment of IBS, it is effective to exert 5-HT_{1A} agonistic action and 5-HT₃ antagonistic action in cooperation. Thus, compounds which are weak in one of these two actions cannot be said to be effective against IBS.

Table 1, shown below, compares the affinity for the 5-HT_{1A} receptor of the compounds of Examples 1-8, 7-28 and 2-8. These compounds are structurally quite identical to one another, except for the substituents on the nitrogen atom at the 3-position of pyrimidine ring.

TABLE A-I, on pages 48-49 of the present specification, shows the affinity for 5-HT_{1A} receptor of only the compound of Example 7-28 from among the above-mentioned three compounds at 10⁻⁷ M. Additionally, the Table gives no data measured at 10⁻⁸ M. Thus, TABLE A-I does not show data of the affinity for the 5-HT_{1A} receptor of the compounds of Examples 1-8 and 2-8. The affinity for the 5- HT_{1A} receptor of each of the compounds in Table 1 below at each concentration has been measured by the method according to “(1) Affinity measurement of the compounds to human 5-HT_{1A} receptor (in vitro)”, on pages 45-46 of the present specification.

Table 1

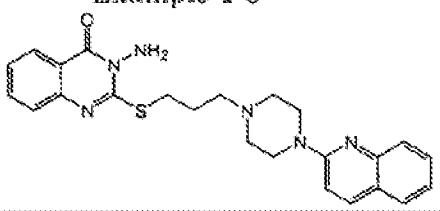
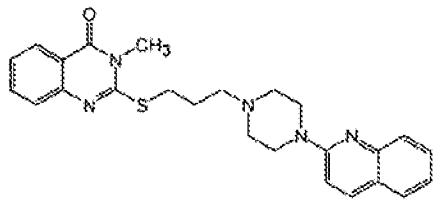
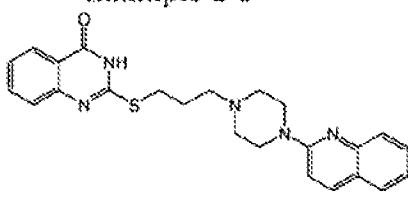
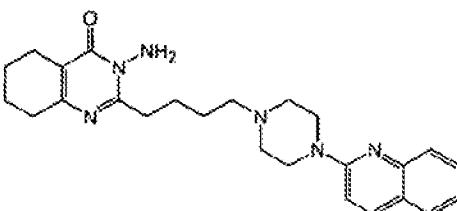
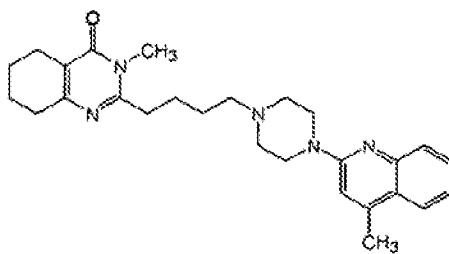
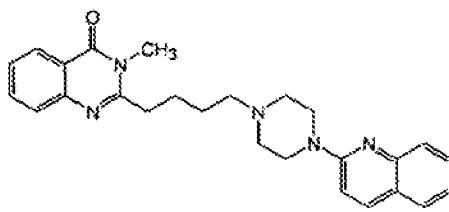
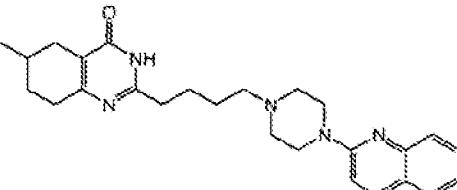
Compound Structure	5-HT _{1A} Binding Inhibition (%)	
	10 ⁻⁷	10 ⁻⁸
Example 1-8 	92.6	41.9
Example 7-28 	74.7	27
Example 2-8 	31	3.8

Table 1 (above) clearly demonstrates that compounds whose nitrogen atom at the 3-position of pyrimidine ring is unsubstituted have a low affinity for 5-HT_{1A} receptor, as compared with compounds whose nitrogen atom at the 3-position of the pyrimidine ring has an amino group or a methyl group.

Further, Table 2, shown below, demonstrates that compounds which are weak in 5-HT_{1A} agonistic action are ineffective against IBS. Applicants acknowledge that unlike in Table 1, the series of compounds in Table 2 are not structurally identical with one another except for substituents on the nitrogen atom at the 3-position of the pyrimidine ring. However, the compounds of Table 2 are structurally similar to one another. Table 2 exhibits the results of animal tests regarding the 5-HT_{1A} agonistic action of said compounds.

Table 2

Compound Structure	5-HT _{1A} Agonistic Activity			
	rat : in vivo agonistic activity		mouse : anti-anxiety	
	dose (mg/Kg)	score	dose (mg/Kg)	effect
Example 4·1 	10 (i.p.)	LLR:1.5 FBP:1.8 BT*1:1.4	3 (i.p.)	+(CFS*2)
Example 7·6 	10 (i.p.)	LLR:2.4 FBP:2.0 BT:1.7	1 (i.p.)	+(CFS)
Example 7·20 	10 (i.p.)	LLR:1.6 FBP:1.8 BT:1.2	3 (i.p.)	+(CFS)
TZB·41044 	30 (i.p.)	LLR:0.2 FBP:1.4 BT:0.9	30 (i.p.)	—(CFS)

*1: Body Temperature, *2: Conditioned Fear Stress

[TZB-41044, the last compound in Table 2, is mentioned for the sake of comparison; it has been produced by the same method as in the present specification.]

Of the scores in the column of "rat: in vivo agonistic activity" in Table 2, LLR and FBP have been measured by "(3) Measurement of 5-HT_{1A} receptor agonistic action on rats (in vivo)", as discussed on page 51 of the present specification. The values of LLR and FBP for Example 4-1, Example 7-6 and Example 7-20 are given in TABLE B-1, on page 52 of the present specification.

"BT", an abbreviation of Body Temperature, means the change in body temperature between before and after the administration of the test compound.

"5-HT_{1A} agonistic action" of the test compound is generally evaluated by the three items of LLR, FBP and BT. (For example, please see The Journal of Pharmacology and Experimental Therapeutics, Vol. 267, pages 58-71, 1993, attached hereto as Exhibit A.)

The first three compounds in Table 2, i.e., Example 4-1, Example 7-6 and Example 7-20, exhibited high values of LLR and FBP and lowered BT to a certain extent. The last compound, TZB-41044, whose nitrogen atom at the 3-position of pyrimidine ring is unsubstituted, showed a small value of LLR and only a slight decrease in BT in spite of large dose. The four compounds in Table 2 are structurally different in the parts other than the substituents on the nitrogen at the 3-position of the pyrimidine ring, and therefore fail to allow precise comparison of one another. From the above experimental results, however, it is presumed that compounds whose nitrogen atom at the 3-position of pyrimidine ring is unsubstituted are weak in 5-HT_{1A} agonistic action.

"CFS" in the column of "effect" of "mouse: anti-anxiety" in Table 2 is an abbreviation for Conditioned Fear Stress. An animal, when it receives a fear stimulus, exhibits a fear reaction and becomes motionless. However, after a certain time, the animal begins to move again. On the other hand, when an animal is given fear stimulus repeatedly under a certain condition, it comes to show fear reaction if only said condition is satisfied. In that case, if an antianxiety agent has been administered to the animal before a fear stimulus is given, the motionless time is reduced.

An animal model which may show a fear reaction under a certain condition may be

prepared. The test compound may be administered beforehand, and the degree of reduction of time from when the condition was given to when the animal began to move again may be determined, thus allowing for an evaluation of the antianxiety action of said compound.

Incidentally, a tricyclic benzodiazepine compound exhibits antianxiety action in low doses. As the dose is increased, however, sedative action reveals itself, and thus, motionless time is prolonged instead of being shortened. 5-HT_{1A} agonists, on the other hand, exhibit increased antianxiety action as higher doses are given, and thus shorten motionless time. This is recognized as an advantage of 5-HT_{1A} agonists.

When CFS was given to mice to which the four compounds of Table 2 had previously been administered respectively, the first three compounds of Table 2 exhibited antianxiety action, whereas the last compound showed no antianxiety action although in a large dose.

The results of Tables 1 and 2, shown above, demonstrate that compounds whose nitrogen atom at the 3-position of pyrimidine ring is unsubstituted are weak in 5-HT_{1A} agonistic action. Thus, these compounds are clearly distinguished in 5-HT_{1A} agonistic action, from compounds whose nitrogen atom at the 3-position of pyrimidine ring has a methyl group.

For the treatment of IBS, it is effective to exert 5-HT_{1A} agonistic action and 5-HT₃ antagonistic action in cooperation. Hence, compounds which are weak in 5-HT_{1A} agonistic action are ineffective against IBS. Therefore, the compounds of the present invention, which are effective against IBS, are clearly distinguished the compound of the cited reference, wherein the nitrogen atom at the 3-position of pyrimidine ring is unsubstituted.

Matsuoka et al. fail to teach or suggest that, for the treatment of IBS, it is effective to exert 5-HT_{1A} agonistic action and 5-HT₃ antagonistic action in cooperation. Furthermore, Matsuoka et al. fail to disclose any compound which has both 5-HT_{1A} agonistic action and 5-HT₃ antagonistic action, and is thus effective against IBS.

For the reasons set forth in detail above, it is evident that the subject matter of Applicants' claims is patentable over the cited reference. Thus, it is respectfully requested that the above-discussed rejection be withdrawn.

Conclusion

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Amendment, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

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